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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
BADIO, BARBARA P	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHEL PAIRET, MICHAEL P. PIEPER,
CHRISTOPHER JOHN MONTAGUE MEADE, RICHARD REICHL,
and CHRISTEL SCHMELZER

Appeal 2011-007772
Application 10/776,757
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and STEPHEN WALSH,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims relating to inhalable powder pharmaceuticals. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The Specification discloses that "an unexpectedly beneficial therapeutic effect, particularly a synergistic effect can be observed in the

treatment of inflammatory or obstructive diseases of the respiratory tract" (Spec. 1: 16-19) if an anticholinergic, such as a tiotropium salt (*id.* at 2: 11-13), is used together with a corticosteroid, such as ciclesonide (*id.* at 2: 28-31).

Claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39, and 63-66 are on appeal. Claim 1 is representative and reads as follows:

> 1. An inhalable powder pharmaceutical composition comprising:
> (a) a tiotropium salt or a hydrate thereof;
> (b) a steroid which is ciclesonide, and
> (c) a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose,
> wherein the tiotropium salt and the steroid are optionally in the form of their enantiomers, mixtures of their enantiomers, or their racemates.

I.

Issue

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 103(a) as being obvious in view of Nishimura,[1] Banholzer,[2] and Keller.[3] The claims have not been argued separately[4] and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

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[1] Koichi Nishimura et al., *Additive effect of oxitropium bromide in combination with inhaled corticosteroids in the treatment of elderly patients with chronic asthma*, 48 ALLERGOLOGY INTERNATIONAL 85-88 (1999)
[2] Banholzer et al., US 5,610,163, Mar. 11, 1997
[3] Keller et al., WO 00/28979, May 25, 2000. Our citations are to the English equivalent of record, US Pat. No 6,645,466 B1, Nov. 11, 2003.
[4] Although the Appeal Brief presents claim 39 under a separate heading, in the form of a separate argument, it incorporates by reference only the same arguments presented for the other claims, and adds no freestanding separate argument. (Appeal Brief 14.)

The Examiner finds that Nishimura discloses "an inhalation composition comprising anticholinergic agents, such as, oxitropium bromide and ipratropium bromide and corticosteroids such as beclomethasone dipropionate for treating asthma" (Answer 3). The Examiner finds that Nishimura discloses that "the addition of oxitropium bromide to beclomethasone dipropionate shows beneficial effects" (*id.* at 3-4).

The Examiner finds that Banholzer discloses "thienyl carboxylic acids such as tiotropium and its salts as strong anticholinergic agents having prolonged action for use in treating asthma" (*id.* at 4). The Examiner finds that Banholzer discloses that "the compounds show similar toxicity to ipratropium bromide while at the same time the therapeutic effect is stronger and prolonged" (*id.*).

The Examiner finds that Keller discloses "dry powder formulations for inhalation … containing a β-mimetic and/or an anticholinergic and/or a corticosteroid" (*id.* at 5). The Examiner also finds that Keller discloses "carriers for … dry powder formulations such as glucose, lactose, sucrose, etc.," tiotropium bromide as an anticholinergic agent, and ciclesonide as a corticosteroid (*id.*).

The Examiner concludes that "a dry powder inhalation formulation comprising an anticholinergic agent, such as a tiotropium salt and a corticosteroid, such as ciclesonide would have been obvious to the skilled artisan" in view of the cited references (*id.* at 6). The Examiner finds that a skilled artisan would have been motivated to combine an anticholinergic agent with a corticosteroid based on "(a) the knowledge in the art of the utilization of each in treating … asthma and (b) the teaching by Nishimura

of the beneficial effect of a combination of an anticholinergic agent and a corticosteroid" (*id.*). The Examiner also finds "motivation to utilize tiotropium as the anticholinergic agent … based on the teaching of Banholzer of [its] stronger and prolonged therapeutic action" (*id.*).

Appellants contend that claim 1 would not have been prima facie obvious in view of the cited references because none of the cited references suggests the specific combination of tiotropium and ciclesonide (Appeal Br. 12-13). Appellants also contend that they have presented evidence of unexpected results that overcomes any prima facie case of obviousness (*id.* at 9-12).

The issues presented are: Does the evidence of record support the Examiner's conclusion that claim 1 would have been prima facie obvious in view of the cited references?

If so, have Appellants provided evidence of unexpected results that outweighs the evidence supporting the prima facie case of obviousness?

Findings of Fact

1. Nishimura discloses that "inhaled corticosteroids are the established treatment of choice in cases of chronic asthma.… The addition of other bronchodilators including … inhaled anticholinergic agents has been recommended in … patients whose asthma is not well controlled." (Nishimura 85, right col.)

2. Nishimura discloses a study to evaluate the "efficacy of the addition of inhaled oxitropium bromide in combination with inhaled corticosteroids in the treatment of elderly asthmatic patients" (*id.*, abstract).

3. Nishimura discloses that the "efficacy of treatment with and without regular inhalation of oxitropium bromide in addition to inhaled BDP [beclomethasone dipropionate] was compared" (*id.* at 86, left col.).

4. Nishimura discloses that "[f]orced expiratory volume in 1 second (FEV_1) was significantly improved after treatment with regular inhalation of oxitropium bromide…. Both morning and evening peak expiratory flow rates were significantly greater during the treatment period with regular inhalation of oxitropium bromide. The score for dyspnea/chest tightness was also significantly improved during the oxitropium bromide period." (*Id.*, abstract.)

5. Banholzer discloses anticholinergic agents that are "useful for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma" (Banholzer, abstract).

6. Banholzer discloses that the anticholinergic agents "have prolonged action. Action lasting at least 24 hours is achieved at inhaled dosages in the μg range.… [T]he toxicity is in the same range as the commercial product Ipratropium bromide while at the same time the therapeutic effect is stronger." (*Id.* at col. 3, ll. 27-32.)

7. The Examiner finds that compound A in column 5 of Banholzer is tiotropium (Answer 4). Appellants do not dispute this finding (*see* Appeal Br. 7).

8. Keller discloses dry powder formulations for inhalation (Keller, col. 4, ll. 44-47) that "comprise a pharmaceutically inactive carrier…, [and] a finely divided pharmaceutically active compound of inhalable particle size" (*id.* at col. 4, ll. 57-63).

9. Keller discloses that the carrier can be, for example, glucose or lactose (*id.* at col. 8, ll. 1-4).

10. Keller discloses that the active compound can be "a beta-mimetic…, an anticholinergic, such as tiotropium, ipratropium, oxitropium or glycopyrronium, [or] a corticosteroid, such as butoxicart, rofleponide, budesonide, ciclesonide…, [or] beclomethasone" (*id.* at col. 6, ll. 13-21).

11. Keller discloses that "the formulations according to the invention can contain two or more pharmaceutically active compounds" (*id.* at col. 6, ll. 36-37).

12. Keller discloses that "dry powder formulations which contain a beta-mimetic and/or an anticholinergic and/or a corticosteroid" (*id.* at col. 6, ll. 52-54).

13. Appellants have provided a declaration under 37 C.F.R. § 1.132 (Declaration of Thierry Bouyssou, filed Nov. 4, 2009).

14. Dr. Bouyssou declares that the "inhibitory effect of tiotropium bromide in combination with ciclesonide on acetylcholine-induced bronchoconstriction over 24 hours after single administration was investigated in comparison to the respective mono-therapies" (Bouyssou Declaration, 3).

15. Dr. Bouyssou declares that "[c]iclesonide applied at 0.1 mg/kg only induced slight bronchoprotection of 5 ± 10 %, 3 hours after drug inhalation which remained constant over 24 hours" (*id.* at 4).

16. Dr. Bouyssou declares that bronchoprotection with tiotropium bromide "reached 35 ± 25 % at 0.06 µg/kg … 3 hours after inhalation. The

compound maintined [sic] at the end of the 24 hour study period a bronchoprotection of 12 ± 7 %" (*id.*).

17. Dr. Bouyssou declares that "[c]ompared to the efficacy of each mono-therapy, the combination of submaximal doses of ciclesonide (0.1 mg/kg) and tiotropium bromide (0.06 µg/kg) resulted in an unexpected super-additive bronchoprotection of 49 ± 7 % at 3 hours and of 41 ± 14 % after 24 hours" (*id.*).

18. Dr. Bouyssou declares that "the synergistic bronchoprotection properties of the combined administration of tiotropium bromide and ciclesonide would not have been expected by those of ordinary skill in the art from the consideration of the Nishimura …; Banholzer …; and Keller references" (*id.*).

Analysis

Claim 1 is directed to an inhalable powder composition comprising a tiotropium salt, ciclesonide, and one of glucose, arabinose, lactose, saccharose, or maltose. Nishimura discloses that treatment with inhaled corticosteroids and inhaled anticholinergic agents has been recommended for patients whose asthma is not well controlled. Nishimura discloses that significant improvement was achieved by adding treatment with oxitropium bromide, an anticholinergic agent, to standard treatment with the corticosteroid beclomethasone dipropionate.

Banholzer discloses that tiotropium is an anticholinergic agent that shows prolonged action, with similar toxicity to the commercial product ipratropium bromide, but with a stronger therapeutic effect. Keller discloses inhalable dry powder formulations which contain a beta-mimetic and/or an

anticholinergic (such as tiotropium) and/or a corticosteroid (such as ciclesonide), and a carrier component that can be glucose or lactose.

In view of these disclosures, it would have been obvious to one of ordinary skill in the art to formulate an inhalable powder pharmaceutical composition comprising tiotropium and ciclesonide in order to take advantage of the combined therapeutic effects of an anticholinergic agent and a corticosteroid as suggested by Nishimura. It would also have been obvious to include glucose or lactose because Keller discloses that they can be used as carrier compounds with inhalable powder formulations, including formulations containing an anticholinergic and a corticosteroid.

Appellants argue that none of the cited references "provide any reason for one of ordinary skill in the art to make the particular combination as claimed" (Appeal Br. 13). Appellants argue that Nishimura discloses a different combination of anticholinergic and steroid than is recited in claim 1 and that Nishimura "is very specific on this particular combination" (*id.*). Appellants further argue that Keller does not discuss the specific combination of claim 1 (*id.*).

This argument is not persuasive. Although Nishimura specifically evaluates the combination of oxitropium bromide and beclomethasone dipropionate, it does not suggest that this specific combination is the only one suitable for treating asthma. Instead, Nishimura discloses that "inhaled corticosteroids," generically, are the established treatment for chronic asthma, and that the addition of "inhaled anticholinergic agents," generically, is recommended for patients whose asthma is not well controlled by corticosteroids alone. Thus, it would have been obvious to use

other corticosteroids and anticholinergic agents in Nishimura's combination treatment method.

Appellants also argue that they have provided evidence of unexpected results that overcomes the asserted case of prima facie obviousness. Appellants argue that the Bouyssou Declaration provides evidence that unexpected synergistic bronchoprotective effects were achieved by the combination of tiotropium and ciclesonide (Appeal Br. 9-12). The Bouyssou Declaration describes a study in dogs with acetylcholine-induced bronchoconstriction in which the bronchoprotective effects of tiotropium combined with ciclesonide was compared with the bronchoprotective effects of the therapeutic agents individually (*see* FFs 14-18).

The Examiner responds that "the combination of an anticholinergic agent and a corticosteroid is taught by the art as evidenced by Nishimura and there is no evidence on record that said results would be unobvious and/or unexpected when compared with the combination taught by Nishimura under similar conditions" (Answer 10).

We agree with the Examiner that Appellants have not provided evidence of unexpected results sufficient to overcome the prima facie case of obviousness. The burden of demonstrating unexpected results rests on the party asserting them. *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). That burden has not been carried here because Appellants have not established that the results shown for the combination of tiotropium and ciclesonide were unexpectedly superior compared to closest prior art, which is the combination of oxitropium bromide and beclomethasone dipropionate disclosed by Nishimura. *See In re Baxter-Travenol Labs.*, 952 F.2d 388,

392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Nishimura discloses that the combination of corticosteroids and anticholinergic agents, generically, is used to treat asthma, and that the combination of oxitropium and beclomethasone, specifically, shows improved benefit compared to beclomethasone alone. Thus, one of skill in the art would have expected that the combination would also be superior to a corticosteroid alone in the acetylcholine-induced bronchoconstriction model cited in the Bouyssou Declaration.

Although the Bouyssou Declaration states that synergistic effect resulted from combining, tiotropium and ciclesonide, a showing of unexpectedly superior results for the claimed combination requires a comparison to the prior art combination of oxitropium bromide and beclomethasone *in the same experimental system*, or at least a showing that those skilled in the art would recognize that the declaratory evidence can be validly compared to the results shown in the prior art.

Here, the Bouyssou Declaration provides no persuasive basis for concluding that Nishimura's results in human asthma patients can validly be compared to the results found in the Bouyssou Declaration for acetylcholine-induced bronchoconstriction in dogs. Thus, the statement in Bouyssou Declaration that the synergistic bronchoprotection properties of the tiotropium/ciclesonide combination "would not have been expected by those of ordinary skill in the art from the consideration of" Nishimura, Banholzer and Keller (FF 18) is not adequately supported by the evidence of record.

Since Appellants have not provided a valid comparison of the claimed combination to the closest prior art, they have not carried the burden of demonstrating unexpected results.

Appellants argue that providing a direct comparison to the closest prior art is not required because "a showing of a synergistic effect of a combination alone can be sufficient proof of nonobviousness" (Reply Br. 1-2; Appeal Br. 4, citing MPEP § 716.02(a)(I)). This argument is not persuasive. The cited portion of the MPEP indicates that unexpected results may be shown by demonstrating a greater than expected result, but goes on to say, consistent with the case law cited above, that "Applicants must further show that the results were greater than those which would have been expected *from the prior art* to an unobvious extent" (MPEP § 716.02(a)(I), emphasis added).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that claim 1 would have been prima facie obvious in view of the cited references. Appellants have not provided evidence of unexpected results that outweighs the evidence supporting the prima facie case of obviousness.

II.

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 103(a) as being obvious in view of Nishimura and Banholzer. We agree with Appellants, however, that "[n]either of Nishimura or Banholzer provide any suggestion to combine the particular steroid ciclesonide" (Appeal Br. 7-8). In articulating this rejection, the Examiner asserted that ciclesonide is a

well-known corticosteroid, but did not cite any evidence to support this assertion. Thus, the Examiner has not met the initial burden of presenting a prima facie case of obviousness based solely on Nishimura and Banholzer.

SUMMARY

We reverse the rejection based on Nishimura and Banholzer. We affirm the rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. § 103(a) in view of Nishimura, Banholzer and Keller.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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